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| 10/517,256                       | 01/14/2005  | Garry George Graham  | 47-216              | 7135             |
| 23117                            | 7590        | 02/01/2010           | EXAMINER            |                  |
| NIXON & VANDERHYE, PC            |             |                      | RAWLINGS, STEPHEN L |                  |
| 901 NORTH GLEBE ROAD, 11TH FLOOR |             |                      | ART UNIT            | PAPER NUMBER     |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

|                              |  |                                      |
|------------------------------|--|--------------------------------------|
| <b>Office Action Summary</b> | <b>Application No.</b><br>10/517,256   | <b>Applicant(s)</b><br>GRAHAM ET AL. |
|                              | <b>Examiner</b><br>Stephen L. Rawlings | <b>Art Unit</b><br>1643              |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
  - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
  - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 04 November 2009.  
 2a) This action is FINAL.      2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1,3,4 and 10-17 is/are pending in the application.  
 4a) Of the above claim(s) 4 and 11-17 is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 1,3 and 10 is/are rejected.  
 7) Claim(s) \_\_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on 07 December 2004 is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- 1) Notice of References Cited (PTO-892)  
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)  
 3) Information Disclosure Statement(s) (PTO/SB/08)  
 Paper No(s)/Mail Date 20091201
- 4) Interview Summary (PTO-413)  
 Paper No(s)/Mail Date. \_\_\_\_\_  
 5) Notice of Informal Patent Application  
 6) Other: PTO-461

**DETAILED ACTION**

***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 4, 2009, has been entered.

1. The amendment filed October 15, 2009, is acknowledged and has been entered. Claims 2 and 6-9 have been canceled. Claims 1 and 10 have been amended.
2. Claims 1, 3, 4, and 10-17 are pending in the application. Claims 4 and 11-17 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on May 1, 2008.
3. Claims 1, 3, and 10 are currently under prosecution.

***Information Disclosure Statement***

4. The information disclosure filed December 1, 2009, has been considered. An initialed copy is enclosed.

***Election/Restrictions***

5. As noted in the preceding Office action mailed April 15, 2009, the restriction and election requirement set forth in the Office action mailed April 1, 2008, the inventions of

Groups II, III, and IV have been rejoined; and thus to that extent the requirement has been withdrawn.

***Priority***

6. Applicant's claim under 35 U.S.C. §§ 119(e) and/or 120, 121, or 365(c) for benefit of the earlier filing date of the benefit of PCT Application No. PCT/AU03/00719, filed June 10, 2003, which claims benefit of Australia Patent Application No. PS 2826, filed June 7, 2002, is acknowledged.

However, claims 1, 3, and 10 are presently rejected under 35 U.S.C. §112, first paragraph, and furthermore, as previously noted, claim 3 does not properly benefit from the earlier filing date of Australia Patent Application No. PS 2826 because that document does not describe the claimed invention. More particularly, it does not disclose that the prostate cancer cells are androgen independent, nor does it describe experiments that utilized androgen independent prostate cancer cell lines, such as PC3.

Accordingly, since this application is the national stage entry of the international application (i.e., PCT Application No. PCT/AU03/00719), the effective filing date of the claims is June 10, 2003 or the filing date of the international application.

***Grounds of Objection and Rejection Withdrawn***

7. Unless specifically reiterated below, Applicant's amendment and/or arguments have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed April 15, 2009.

***Grounds of Rejection Maintained***

***Claim Rejections - 35 USC § 112***

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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9. The rejection of claims 1, 3, and 10 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is maintained.

Beginning at page 8 of the amendment filed October 15, 2009, Applicant has traversed the propriety of maintaining this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Claims 1, 3, and 10 are indefinite for the following reasons:

As presently amended, claim 1 recites "an sPLA<sub>2</sub>-IIA polypeptide having a sequence as defined in SEQ ID NO: 3"; this recitation is not read a limitation that the polypeptide to which the claims are directed is a polypeptide comprising the amino acid sequence of SEQ ID NO: 3. Instead this recitation is interpreted to mean that the polypeptide may have any sequence contained within (and defined by) the sequence of SEQ ID NO: 3. A sequence is any two contiguous amino acids. As such the claims are presently directed to any of a large plurality of structurally (and functionally) different polypeptides having amino acid sequences comprising at least two contiguous amino acids of the amino acid sequence set forth as SEQ ID NO: 3.

It is for these reasons that the amendment has not remedied the issue that is raised by this rejection in the preceding Office actions.

Here, it is apparent that the claims do not clearly and particularly identify the "sPLA<sub>2</sub>-IIA" polypeptide(s) that are necessarily targeted by the inhibitor, so that inhibition of the activity of the polypeptide(s) results in the inhibition or reduction in the proliferation of prostate cancer cells and/or therapeutic effect.

Although claim 10, for example, describes the inhibitor as having a very particular structure, the claims are drawn to a method of inhibiting or reducing the proliferation of prostate cancer cells that express "sPLA<sub>2</sub>-IIA" by administering to these cells the inhibitor. It is therefore imperative that the identity of the cells be established in order to practice the claimed invention. If the cells are only described as prostate cells

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expressing "sPLA<sub>2</sub>-IIA", but the polypeptide is not clearly and particularly described, the artisan could not know or determine to which cells the inhibitor must be administered.

Therefore, because 35 U.S.C. § 112, second paragraph, requires the claim define the metes and bounds of the subject matter that is regarded as the invention with such clarity and particularity to permit the skilled artisan to know or determine infringing subject matter, and because the term used to describe the polypeptides to which the claims are directed do not unambiguously identify those polypeptides, this requirement has not been met.

*It is suggested that this issue could be remedied at least in part by amending claim 1 to recite, for example, "an sPLA<sub>2</sub>-IIA polypeptide having the amino acid sequence of SEQ ID NO: 3".*

If such an amendment were made, it would be evident that the sPLA<sub>2</sub>-IIA polypeptide to which the claims are directed is a polypeptide comprising the entirety of the amino acid sequence of SEQ ID NO: 3 and as such, the claims would clearly and particularly identify the polypeptide by its primary structure.

Even so, as explained in the preceding Office action, because the "sPLA<sub>2</sub>-IIA" polypeptide(s) to which the claims are directed have more than one function, it may not be sufficient to merely identify the polypeptide(s), but might instead be imperative that the activity that must be inhibited by the inhibitor is identified.

For this reason, because claim 1 has been amended to recite, "the enzyme activity of an sPLA<sub>2</sub>-IIA polypeptide", and since there are more than one such polypeptide (enzyme) having more than one enzymatic activity, it cannot be determined to which enzymatic activity (or to which polypeptide) the claims refer.

Again, which one the plurality of activities of "sPLA<sub>2</sub>-IIA" must be inhibited in order to inhibit or reduce the proliferation of prostate cancer cells? Which activities must be inhibited by the inhibitor, such that the inhibitor is used to treat prostate cancer in a subject?

To be clear, here, the issue at hand is whether or not the use of the term "sPLA<sub>2</sub>-IIA" clearly and particularly identifies the polypeptides that must be inhibited by the inhibitor to which the claims are directed, such that the process may be practiced to

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achieve the claimed objective, namely the inhibition or reduction of the proliferation of prostate cancer cells and/or the treatment of prostate cancer in a subject. As evidenced by the disclosure of Markova et al. (of record), for example, the term describes not a single polypeptide, but a plurality of structurally differing polypeptides, which have, at least in the models used by Markova et al., different functions.

Furthermore, it is not evident which cases of prostate cancer are caused by the presence of prostate cancer cells that express "sPLA<sub>2</sub>-IIA" because, in part, it is not evident to which polypeptide the term "sPLA<sub>2</sub>-IIA" refers.

How might the artisan know or determine if a prostate cancer is caused by the presence of prostate cancer cells that express "sPLA<sub>2</sub>-IIA", if the identify of the polypeptide is not known or cannot be determined?

It would seem that this latter issue would be best remedied by amending claim 1 to recite, for example, a limitation that the selective inhibitor is capable of inhibiting the ability of the polypeptide to "catalyse the hydrolysis of membrane phospholipids at the sn-2 position to release fatty acids and lysophospholipids", as described by the specification at, e.g., paragraph [0005] of the published application, if indeed that need be the case.

Accordingly, it is submitted that this ground of rejection would be obviated if Applicant were to amend claim 1 to read as follows:

1. (Currently Amended). A method of inhibiting or reducing the proliferation of prostate cancer cells that express a sPLA<sub>2</sub>-IIA polypeptide comprising the amino acid sequence of SEQ ID NO: 3 in a human subject in need thereof, the method comprising administering to the cells subject a selective inhibitor of the enzyme activity of an sPLA<sub>2</sub>-IIA the polypeptide having a sequence as defined in SEQ ID NO: 3, wherein the inhibitor inhibits the ability of the polypeptide to catalyse the hydrolysis of membrane phospholipids at the sn-2 position to release fatty acids and lysophospholipids, wherein the inhibitor inhibits the sPLA<sub>2</sub>-IIA-mediated proliferation of prostate cancer cells, and wherein the inhibitor is a cyclic peptide of the following formula:

A1-A2-A3-A4-A5, in which

A1 is F or Y or W or 2Nap<sub>1</sub>

A2 is L or I<sub>1</sub>

A3 is S or T<sub>1</sub>

A4 is F or Y or W or 2Nap<sub>1</sub>, and

A5 is R or K.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. The rejection of claims 1, 3, and 10 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Beginning at page 9 of the amendment filed October 15, 2009, Applicant has traversed the propriety of maintaining this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, "Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <<http://www.gpoaccess.gov/>>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless,

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these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

*Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). See also: *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention*.

In this instance, the claims are drawn to a method of inhibiting or reducing the proliferation of prostate cancer cells and/or treating prostate cancer in a subject.

Although claim 10, for example, describes the inhibitor as having a very particular structure, the claims are drawn to a method of inhibiting or reducing the proliferation of prostate cancer cells that express "sPLA<sub>2</sub>-IIA" by administering to these cells the inhibitor. It is therefore imperative that the identity of the cells be established in order to practice the claimed invention. If the cells are only described as prostate cells expressing "sPLA<sub>2</sub>-IIA", but the polypeptide is not clearly and particularly described, the artisan could not know or determine to which cells the inhibitor must be administered and consequently the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention as of the time the application was filed in order to satisfy the written description requirement.

As presently amended, claim 1 recites "an sPLA<sub>2</sub>-IIA polypeptide having a sequence as defined in SEQ ID NO: 3"; this recitation is not read a limitation that the polypeptide to which the claims are directed is a polypeptide comprising the amino acid sequence of SEQ ID NO: 3. Instead this recitation is interpreted to mean that the polypeptide may have any sequence contained within (and defined by) the sequence of SEQ ID NO: 3. A sequence is any two contiguous amino acids. As such the claims are presently directed to any of a large plurality of structurally (and functionally) different polypeptides having amino acid sequences comprising at least two contiguous amino acids of the amino acid sequence set forth as SEQ ID NO: 3.

Nevertheless, because the "sPLA<sub>2</sub>-IIA" polypeptide(s) to which the claims are directed have more than one function, it is not sufficient to merely identify the polypeptide(s) by describing its structure.

Which one the plurality of (enzymatic) activities of "sPLA<sub>2</sub>-IIA" must be inhibited in order to inhibit or reduce the proliferation of prostate cancer cells? Which activities must be inhibited by the inhibitor, such that the inhibitor is used to treat prostate cancer in a subject?

Here, the issue at hand is whether or not the use of the term "sPLA<sub>2</sub>-IIA" clearly and particularly identifies the polypeptides that must be inhibited by the inhibitor to which the claims are directed, such that the process may be practiced to achieve the claimed objective, namely the inhibition or reduction of the proliferation of prostate

cancer cells and/or the treatment of prostate cancer in a subject. As evidenced by the disclosure of Markova et al. (of record), for example, the term describes not a single polypeptide, but a plurality of structurally differing polypeptides, which have, at least in the models used by Markova et al., different functions.

Furthermore, it is not evident which cases of prostate cancer are caused by the presence of prostate cancer cells that express "sPLA<sub>2</sub>-IIA" because, in part, it is not evident to which polypeptide the term "sPLA<sub>2</sub>-IIA" refers.

How might the artisan know or determine if a prostate cancer is caused by the presence of prostate cancer cells that express "sPLA<sub>2</sub>-IIA", if the identify of the polypeptide is not known or cannot be determined?

For all of the above reasons, although Applicant's arguments have been carefully considered, it is submitted that the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed, so as to satisfy the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

Accordingly, it is submitted that this ground of rejection would be obviated if Applicant were to amend claim 1 to read as follows:

1. (Currently Amended). A method of inhibiting or reducing the proliferation of prostate cancer cells that express a sPLA<sub>2</sub>-IIA polypeptide comprising the amino acid sequence of SEQ ID NO: 3 in a human subject in need thereof, the method comprising administering to the cells subject a selective inhibitor of the enzyme activity of an sPLA<sub>2</sub>-IIA the polypeptide having a sequence as defined in SEQ ID NO: 3, wherein the inhibitor inhibits the ability of the polypeptide to catalyse the hydrolysis of membrane phospholipids at the sn-2 position to release fatty acids and lysophospholipids, wherein the inhibitor inhibits the sPLA<sub>2</sub>-IIA-mediated proliferation of prostate cancer cells, and wherein the inhibitor is a cyclic peptide of the following formula:

A1-A2-A3-A4-A5, in which

A1 is F or Y or W or 2Nap<sub>1</sub>

A2 is L or I<sub>1</sub>

A3 is S or T,

A4 is F or Y or W or 2Nap, and

A5 is R or K.

12. The rejection of claims 1, 3, and 10 under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for using** a method for inhibiting or reducing the proliferation of prostate cancer cells, which express a human sPLA<sub>2</sub>-IIA polypeptide comprising the amino acid sequence of SEQ ID NO: 3 and having an activity that is inhibited by the particularly described inhibitors "cFLSYR" and "c(2Nap)LS(2Nap)R", in a human subject, said method comprising administering to the subject an amount of a selective inhibitor of said human sPLA<sub>2</sub>-IIA polypeptide effective to inhibit or reduce the proliferation of said prostate cancer cells in the subject, wherein said inhibitor is a cyclic peptide of the following formula:

A1-A2-A3-A4-A5, in which

A1 is F or Y or W or 2Nap,

A2 is L or I,

A3 is S or T,

A4 is F or Y or W or 2Nap, and

A5 is R or K,

and **while being enabling for using** any process that is encompassed by the claims, which is taught by the prior art, **does not reasonably provide enablement for using** the claimed methods, is maintained. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Beginning at page 10 of the amendment filed October 15, 2009, Applicant has traversed the propriety of maintaining this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

For reasons explained in detail in the preceding Office action it is again submitted that the amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

The specification describes a method for inhibiting the proliferation of certain human prostate cancer cells, such as PC-3 and LNCaP, which express a human sPLA<sub>2</sub>-IIA having an activity that is inhibited by the particularly described inhibitors "cFLSYR" and "c(2Nap)LS(2Nap)R", which are analogues of the linear peptide consisting of SEQ ID NO: 5 (F-L-S-K-Y), as described by Tseng et al. (*J. Biol. Chem.* 1996 Sep 27; **271** (39): 23992-23998) (of record).

The specification discloses that the cyclic peptides designated "cFLSYR" and "c(2Nap)LS(2Nap)R" are capable of inhibiting the proliferation of two prostate cancer cell lines, namely LNCaP and PC-3, but incapable of inhibiting another (i.e., DU-145); see, e.g., Figure 4.

Nonetheless, it is now submitted that at best the specification would reasonably enable the skilled artisan to use a method for inhibiting or reducing the proliferation of prostate cancer cells in a human subject, which express a human sPLA<sub>2</sub>-IIA polypeptide comprising the amino acid sequence of SEQ ID NO: 3 and having an activity that is inhibited by the particularly described inhibitors "cFLSYR" and "c(2Nap)LS(2Nap)R", said method comprising administering to the subject an amount of a selective inhibitor of said human sPLA<sub>2</sub>-IIA polypeptide effective to inhibit or reduce the proliferation of said prostate cancer cells in the subject, wherein said inhibitor is a cyclic peptide of the following formula:

A1-A2-A3-A4-A5, in which  
A1 is F or Y or W or 2Nap,  
A2 is L or I,  
A3 is S or T,  
A4 is F or Y or W or 2Nap, and  
A5 is R or K.

In conclusion, though Applicant's arguments have been carefully considered, upon equally careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), it has been determined that the amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not have been sufficient to have enabled the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

***New Grounds of Rejection***

***Claim Rejections - 35 USC § 103***

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

14. Claims 1, 3, and 10 are rejected under 35 U.S.C. 103(a), as being unpatentable over Graff et al. (*Clin. Cancer Res.* 2001 Dec; **7**: 3857-3861) (of record; cited by Applicant) in view of Church et al. (*J. Biol. Chem.* 2001 Aug 31; **276** (35): 33156-33164) (of record), Attiga et al. (*Cancer Res.* 2000 Aug 15; **60**: 46-29-4637) (of record; cited by Applicant), Liu et al. (*J. Urol.* 2000 Sep; **164**: 820-825) (of record), or Kelavkar et al. (*Carcinogenesis*. 2001 Nov; **22** (11): 1765-1773) (of record).

Graff et al. teaches the expression of the gene encoding human sPLA<sub>2</sub>-IIA is specifically increased with progression of human prostate cancer cells to androgen independence; see entire document (e.g., the abstract). Graff et al. teaches the expression of sPLA<sub>2</sub>-IIA is inversely related to patient survival; see, e.g., the abstract. Accordingly, Graff et al. teaches their report "provides compelling evidence that enhanced sPLA2-IIa expression may be involved in the malignant progression of human

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prostate cancer and suggests that specific inhibitors of the group IIa sPLA2 may be useful for prostate cancer chemotherapy" (page 3860, column 2).

Accordingly, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have inhibited the growth or proliferation of prostate cancer cells by contacting the cells with an agent that inhibits the expression and/or activity of human sPLA<sub>2</sub>-IIA in prostate cancer cells. One ordinarily skilled in the art at the time the invention was made would have been motivated to do so in order to treat prostate cancer.

However, Graft et al. does not expressly teach or suggest that the sPLA2-11A inhibitor is a cyclic peptide or analogue derived from the linear peptide first described by Tseng et al. (*supra*), which is a peptide consisting of the amino acid residues at positions 70-74 of a purified human sPLA2-11A protein.

Nevertheless, Church et al. describes the identification of a peptide consisting of the amino acid residues at positions 70-74 of a purified human sPLA<sub>2</sub>-IIA protein, which is capable of inhibiting the catalytic activity of sPLA<sub>2</sub>-IIA; see entire document (e.g., the abstract). Church et al. teaches this peptide, first described by Tseng et al. (*supra*), consists of the amino acid sequence: F-L-S-Y-K; see, e.g., the abstract. Church et al. teaches cyclization of the peptide or of an analogue (i.e., F-L-S-Y-R) increased the inhibitory potency of the peptide, as compared to the original peptide; see, e.g., page 33161, column 2. However, Church et al. further discloses that a cyclic analogue of the peptide in which the phenylalanine and tyrosine residues are replaced by 2-naphthylalanine is even more potent; see, e.g., page 33161, column 2. Church et al. designates this cyclic analogue: "c(2NapA)LS(2NapA)R"; see, e.g., page 33162, Table II.

Accordingly, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have inhibited the growth or proliferation of prostate cancer cells by contacting the cells with the cyclic peptides described by Church et al., which were demonstrated to be highly potent inhibitors of sPLA<sub>2</sub>-IIA, such as the peptide designated by Church et al. as "c(2NapA)LS(2NapA)R". One ordinarily

skilled in the art at the time the invention was made would have been motivated to do so in order to treat prostate cancer.

One ordinarily skilled in the art at the time the invention was made would have had a reasonable expectation of successfully doing so in light of the disclosure of Attiga et al., Liu et al., or Kelavkar et al.

Attiga et al. teaches eicosanoids modulate the interaction of tumor cells with various host components in cancer metastasis, and their synthesis involves the release of arachidonic acid from cellular phospholipids by phospholipase A<sub>2</sub>, followed by metabolism by cyclooxygenases and lipoxygenases; see entire document (e.g., the abstract). Attiga et al. teaches the invasion of prostate cancer cells (i.e., PC-3 and DU-145 cells) is inhibited by a PLA2 inhibitor, a general cyclooxygenase inhibitor, and a selected COX-2 inhibitor; see, e.g., the abstract. Attiga et al. teaches treatment of the cells with these inhibitors reduced their secretion of matrix metalloproteinases; see, e.g., the abstract.

Liu et al. teaches the growth of PC-3 xenograft tumors in nude mice was inhibited by a COX-2 inhibitor; see entire document (e.g., the abstract). Liu et al. teaches COX-2 inhibition is even more effective *in vivo* than might be predicted because treatment of prostate cancer cells with the inhibitor induces the cells to undergo apoptosis and causes down-regulation of the gene encoding VEGF, so as to have anti-angiogenic effects; see, e.g., page 820, column 2.

Kelavkar et al. teaches the gene encoding 15-lipoxygenase-1 is overexpressed in PC-3 prostate cancer cells, and that aberrant expression of enzymes that convert unsaturated fatty acid arachidonic acid and linoleic acid to bioactive lipid metabolites appears to significantly contribute to the development of prostate cancer; see entire document (e.g., the abstract; and page 1765, column 2). Kelavkar et al. teaches that overexpression of 15-lipoxygenase-1 by PC-3 cells leads to the up-regulation of the gene encoding VEGF; see, e.g., page 1771, column 2. Kelavkar et al. teaches that the proliferation of PC-3 cells is inhibited by treating the cells with an inhibitor of 15-lipoxygenase-1; see, e.g., the abstract.

Thus, in view of the disclosures of Attiga et al., Liu et al., or Kelavkar et al., one ordinarily skilled in the art at the time the invention was made would have had a reasonable expectation of successfully practicing the claimed invention because PLA<sub>2</sub> (e.g., sPLA<sub>2</sub>-IIA) acts upstream of the cyclooxygenases and lipoxygenases, which in turn act to convert unsaturated fatty acid arachidonic acid and linoleic acid to bioactive lipid metabolites that contribute to the development of prostate cancer. Because inhibition of the cyclooxygenases and lipoxygenases has proven effective to inhibit the proliferation of prostate cancer cells, as well as the spread of the cancer by anti-angiogenic mechanisms, the artisan would reasonably expect that the inhibition of sPLA<sub>2</sub>-IIA in prostate cancer cells will result in the inhibition of their proliferation by inhibiting the activities of the cyclooxygenases and lipoxygenases acting downstream of PLA<sub>2</sub> in the pathway leading to the production of the eicosanoids, such as prostaglandins and leukotrienes, as well as in the regulation of the gene encoding VEGF. Then, because Church et al. describes the identification of a peptide consisting of the amino acid residues at positions 70-74 of a purified human sPLA<sub>2</sub>-IIA protein, which is capable of inhibiting the catalytic activity of sPLA<sub>2</sub>-IIA, one of skill in the art at the time the invention was made would have had a reasonable expectation of successfully using the claimed process to inhibit or reduce the proliferation of prostate cancer cells that express sPLA<sub>2</sub>-IIA, which depends at least in part upon the activity of the enzyme.

### ***Conclusion***

15. No claim is allowed.
  
16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Stephen L. Rawlings/  
Primary Examiner, Art Unit 1643

slr  
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